AMERICAN

# Journal of Pharmacy

AND THE SCIENCES SUPPORTING PUBLIC HEALTH

DR. W. PAUL BRIGGS
1957 Remington Medalist

*Since 1825* *September 1957*

American Journal of Pharmacy

Published monthly by the Philadelphia College of Pharmacy and Science
43d Street, Kingsessing and Woodland Avenues, Philadelphia 4, Pa.

Annual Subscription $4.00 — Foreign Postage, 25 Cents Extra
Single Numbers, 40 Cents — Back Numbers, 50 Cents

Entered as Second-Class Matter March 27, 1937, at the Post Office at Philadelphia, Pa.
Under Act of March 3, 1879

# New Chemotherapy

# OF RHEUMATOID ARTHRITIS

- RELIEF AND RENEWED HOPE FOR OVER 4,000,000 PATIENTS
- EXTRA PROFITS FOR YOUR PRESCRIPTION DEPARTMENT

**Long-term treatment with ARALEN® has proved strikingly successful in over 70% of cases. "Major improvement" occurred often when other agents had failed.**

**The high incidence of rheumatoid arthritis in all parts of the nation and the extremely successful results achieved with ARALEN indicate an instant and constantly growing demand for this product.**

ARALEN demand in your pharmacy area will be encouraged and promoted by intensive detailing and advertising.

**STOCK UP NOW** on both sizes.
The demand will be immediate and heavy.

# ARALEN® Phosphate

Winthrop LABORATORIES 1450 Broadway, New York 18, N.Y.

250 mg. tablets, bottles of 100 and 1000
125 mg. tablets, bottles of 100

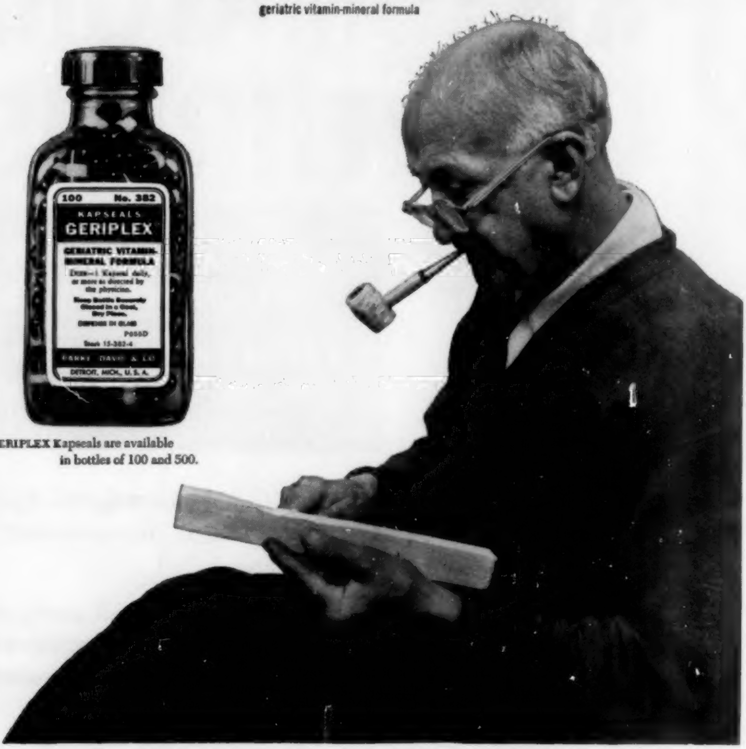
ARALEN (brand of chloroquine) trademark reg. U.S. Pat. Off.

## They keep coming back for more!

# GERIPLEX®

## KAPSEALS®

geriatric vitamin-mineral formula




GERIPLEX Kapseals are available in bottles of 100 and 500.

Chances are when you fill a prescription for GERIPLEX KAPSEALS you've got a customer for life. More and more physicians are prescribing this vitamin-mineral supplement as long-term therapy for their geriatric patients. Containing valuable mineral nutrients, eight important vitamins, and Taka-Diastase® for starch digestion, GERIPLEX helps to correct nutritional deficiencies leading to premature debility.

Service your customers by keeping an adequate supply of GERIPLEX in stock.

PARKE, DAVIS & COMPANY DETROIT 32, MICHIGAN

# AMERICAN JOURNAL OF PHARMACY

## AND THE SCIENCES SUPPORTING PUBLIC HEALTH

Since 1825



Vol. 129 SEPTEMBER 1957 No. 9

CONTENTS

# OUR COVER

## DR. W. PAUL BRIGGS
## 1957 Remington Medalist

THE selection of Dr. W. Paul Briggs to receive the 1957 Remington Honor Medal is an honor well deserved. For years, he has been recognized as one of American Pharmacy's clear-thinking leaders and one who has consistently worked to bring pharmacy greater professional recognition. In recent years, his outstanding efforts in behalf of pharmaceutical education have done much to make possible the improved standards and teaching so evident in our colleges of pharmacy.

Dr. Briggs is himself a trained pharmacist having graduated from the School of Pharmacy at George Washington University. He later did graduate work at the University of Maryland and then returned to the School of Pharmacy at George Washington University to become a member of the staff. From 1932-47, he was Dean at this school although, during part of this time, he saw service in the United States Navy rising to the rank of Commander. After the war, he became Director of the Pharmacy Division of the Veterans Administration and had much to do with arranging the details whereby the interests of pharmacy in its relation to the Veterans Administration were fully protected. From 1948-51, Dr. Briggs discharged similar duties as head of the Pharmacy Service of the Medical Service Corps of the United States Navy.

Since this time, he has been the Secretary and Executive Director of the American Foundation for Pharmaceutical Education. In this capacity, he has done much in building the Foundation to its present strength and has made possible its many important services to our colleges of pharmacy and other related organizations. Dr. Briggs is Treasurer of the *United States Pharmacopeia* and a member of its Board of Trustees.

Dr. Briggs as the thirty-fourth recipient of the Remington Honor Medal will be receiving Pharmacy's highest award. He has truly devoted all his life toward the advancement of pharmacy on the highest plane. He has understood its needs and worked diligently in many circles to see that they were provided for. He has been and continues to be a clear-thinking, forthright leader—the kind which our profession needs and can well afford to honor.

# E D I T O R I A L

## FOREIGN PRESCRIPTIONS

ONE of the most bothersome problems confronting pharmacists, particularly along the Eastern seaboard, is the foreign prescription. These invariably are original prescriptions or a copy originating in some eastern European country. In some cases, they are presumably for medication to be taken by a person now residing in the United States while, in others, they are to be sent overseas for the benefit of some person who either cannot obtain the drug there or cannot afford it.

The pharmacist receiving such a prescription is at the outset confronted with the almost impossible task of deciphering just what drug is wanted. While the handwriting of physicians is notoriously poor, when it is in some foreign script as well as a foreign language, it is almost unintelligible. It would be interesting to know how many mistakes are made on this basis alone. Those pharmacists who realize their inability to decipher the prescription usually send it to some neighboring college of pharmacy, particularly if such college happens to have some European-trained teachers on its staff. This usually leads to a fairly accurate translation of both the identity of the drug specified and the directions, but it does not solve an even larger problem which does not seem to be given adequate attention.

We seriously doubt both the propriety and the legality of filling a prescription when both the identity of the patient as well as that of the prescriber are unknown to the pharmacist. In many cases, it is not even certain that the prescription has been written by a bona fide physician licensed to practice in his own country. It has always been a part of our philosophy that a pharmacist has the responsibility of being certain that any given prescription has been written by a duly licensed physician and that the medication prescribed is to be administered in proper dosage with the ultimate safety of the patient not disregarded. These prerequisites of proper prescription practice cannot possibly be fulfilled with most foreign prescriptions.

To make matters still worse, the prescription—after it is filled—is usually turned over to some layman to be sent to a friend or relative overseas. In so doing, the pharmacist places a prescription-

legend drug in the hands of some person not entitled by law to receive it. There is no guarantee whatsoever that the drug will be sent overseas and not misdirected into some improper channel.

We call attention to this growing problem not because we are unsympathetic with the critical needs of many distressed and pathetic people who are not as fortunate as we ourselves. There does seem to be, however, some need for more precise regulations governing this traffic in drugs or, if there be such regulations now in existence, they surely need to be given wider publicity and enforcement. As matters now stand, it is entirely possible for a layman in some European country to write himself a prescription, send it to some relative in the United States, have it filled in a pharmacy, and have it sent back to him—and all of this done without any medical supervision whatsoever. Such lack of control is basically wrong and contrary to the principles underlying the Food, Drug and Cosmetic Act.

L. F. Tice

# GLASSWARE WASHING OPERATIONS IN BIOLOGICAL AND STERILE PHARMACEUTICAL PRODUCTION *

By E. S. Barclay **

## Glassware Washing

THE purpose of the glassware operation is to develop the best and most economic technics to deliver suitable glassware to the laboratory worker.

The operations we will describe are closely connected with the biological industry and will necessarily involve reference to sterilizing operations which are closely coupled to our manufacturing procedures. We are sure many of the factors involved in a glassware operation covered by this discussion will not include all of your problems.

As we see it, these are some of the problems we face daily—

1. The washing of intricate and expensive pieces of specialized glassware.

2. The washing of calibrated items.

3. The washing of "special situation" glassware—requiring the recognition of the various types of work being done in the laboratory (acid wash, siliconing, etc.).

4. Economic handling of large volume items of all types.

5. The avoidance of spoilage of items by scratching, chipping, etching, and, of course, breakage during the washing operation.

6. The washing and use of the proper closure, whether it be glass, rubber, foil, paper, cotton, gauze, loose fitting aluminum caps, cases for pipettes, cases for petri dishes, etc.

7. Washing and treatment of the carrying containers.

8. The washing of final container glassware as received from the glassware manufacturer.

---

* Presented at the Conference on Preparation of Parenteral Products by the Hospital Pharmacist, New York City, April 27, 1957.

** Director Biological Laboratories, Merck Sharp & Dohme, Division of Merck & Co., Inc., Philadelphia & West Point, Penna.

We will attempt to discuss these operations in some logical sequence in order that each of you having a particular problem will be able to follow, at least generally, our methods of operation.

In our operations we use what is known as a "Standard Method Letter", which describes in detail the handling of each type of glassware and the preparation of any components which normally accompany that piece of glassware. In this way, we believe that confidence and consistency in the glassware operation can be attained.

In setting up such an operation, whether a small kitchen or a large washroom involving thousands of square feet, it is well to avoid the use of averages in calculating the space or equipment requirements. For example—we could say the average weight of a cow and a rabbit is 800 pounds, but this would not tell us much about the size of either.

You are all acquainted with the maximum or "peak" loads which have to be handled in your laboratories during certain days of the week. If the equipment cannot handle these loads, confusion and lost motion is abundant.

The alternative is excessively high inventories of glassware and the space associated with holding this inventory. At today's prices for space, sometimes quoted at $40. to $80. per square foot, it seems to us that it makes more sense to buy equipment which can handle your peak loads.

We believe that the glassware washroom is the heart of the laboratory operation—without it no work gets done—but with proper planning and operation a steady flow of usable items emerges.

If a high percentage of the glassware is contaminated, the washing operation should be situated near the sterilizer to eliminate excess handling and take advantage of the residual heat and moisture of the autoclave.

In our particular location, water is a serious economic consideration. Each drop of water used in our West Point operations must be treated before it arrives at the point of use.

Other economic considerations, such as the detergents, washing compounds, chemicals, etc., make it necessary to calibrate each of the tanks, sinks, or washing vessels used for dilution of the washing compounds. Furthermore, we also supply measuring scoops for washing compounds, that, by test, deliver the optimum amount of chemical for the best washing conditions. This, we believe, removes the "guess-work" in charging each vessel in preparing the washing solutions.

In selecting an area for discussion today, we felt that a good example of an all-around washing operation would be those operations of the Poliomyelitis Vaccine Unit. In this unit all soiled glassware returned to the washing area is considered to be contaminated and must be sterilized by autoclave at 250° F. for a period of 20 minutes before going through the cleaning processes. For this operation we use a Better Built "Hydro" Washer.

In our opinion the Better Built "Hydro" Washer is the most versatile glassware washer on the market today. The range of sizes handled and consistency of treatment provide volume and quality that is impossible to achieve with hand washing or any other washer, plus the occupancy of a relatively small area.

*Better Built "Hydro" Washer*— 27′ long × 4′ 6″ wide, having 138—4-place carrier arms with 7 types of racks capable of handling glassware from a ⅜ × 5 culture tube to a 45 liter bottle. Wash tank has capacity of 450 gallons and is charged with 25 lbs. of "Aura" Detergent.

A complete cycle consisting of the following treatment takes 15 minutes.

a. Pre-rinse by reclaimed water under pressure 3 times.

b. Ten inside hot (180° F.) detergent treatments under high pressure. Also, a sufficient number of overhead and outside treatments of hot detergent.

c. Four preliminary inside and outside rinses of hot (150° F.) reclaimed water under pressure.

d. Three final inside and outside rinses of hot tap water.

e. One inside distilled water rinse.

f. One inside distilled deionized water rinse.

g. A five minute hot air drying cycle.

After subjecting all of the glassware to the above treatment, we are assured of complete uniform washing, rinsing, and drying.

Glassware is inspected and either wrapped with brown paper and aluminum foil or covered with an aluminum cap as required. Glassware is placed in trays and arranged on truck for sterilization by Dry Wall method at 356° F. for 3 hours.

*Fisher Washer*—Wassermann Tubes (with oil)
Roller Tubes

All tubes are packed in baskets which hold from 350 to 500 depending on size. Care is exercised in the packing and washing to eliminate mixing of those tubes containing oil and those free of oil scum.

The treatment described below has proven to be the most efficient for eliminating the oil scum prior to subjecting the tubes to the normal wash cycle.

Washer is filled to the overflow pipe with tap water while the baskets are being secured to the rotary drum by the lids. One ounce of Pink "Dreft", a common household detergent, is added. "Steam jets" and steam coil valves are turned on and washer is put in motion. After temperature of water reaches 212° F., tubes are washed for 5 minutes. Drain valve is opened, "steam jets" valve is closed, and while water is draining out, hot tap water is sprayed over the baskets to eliminate the foaming. When wash water is completely removed the drain is closed and a continuous tap water rinse is given, allowing the water to go out the overflow for approximately 3 minutes. Washer is drained and the following wash cycle which applies to all types of tubes is begun.

a. "Aura" Detergent—1% solution—
Boil—5 minutes

b. "Duponol C"—0.5% solution—
150° F.—3 minutes

c. Tap water rinse—
150° F.—2 × 5 minutes

d. Distilled water rinse—
150° F.—2 × 5 minutes

e. Deionized Distilled water rinse—
180° F.—3 minutes

Baskets are removed from washer and placed in a drying oven for approximately 20 minutes or until completely dry. When tubes are dry baskets are delivered to packing area, cooled, inspected, packed 1000 per tray, wrapped with double thickness of brown paper and placed on truck for sterilization by the Electric Dry Wall method for a period of 3 hours at 356° F. (180° C.) .

*Better Built Turbomatic Washer*—Miscellaneous glassware containing oil
50 ml. to 1250 ml. bottles
5 liter Povitsky bottles
Flasks

The Turbomatic Washer is completely automatic having a timing device which controls the various treatments. Water is circulated by a high pressure and high volume pump. All valves are mechanically opened and closed.

Two types of headers are used:

1. 110 place spindle-type for small tubes and glassware
2. 12 place spray nozzle-type for 5 liter Povitsky bottles

Washer is charged with 4 ounces of "Aura" detergent, or in the case of glassware containing oil, one ounce of Pink Dreft.

Glassware is loaded on spindles and header is pushed into place, the door is closed and completes the electrical circuit when handle is locked in position. Washer is set in motion by pushing the starting button. The full washing cycle described below takes approximately 7 minutes.

a. Pre-wash rinse of reclaimed water.

b. Wash Cycle—Detergent is added at this point, to 180° F. tap water. Wash water is forced into and over glassware by circulating pump..

c. Tap water rinse—180° F. temperature under pressure.

d. Distilled water rinse—180° F. temperature under pressure.

e. Deionized distilled water rinse—180° F. temperature under pressure.

By turning a "hold" switch the cycle may be interrupted and held on that phase until the operator desires to continue the cycle.

When oil soiled glassware has been washed using Pink Dreft it is necessary to re-wash with Aura, on the Turbcmatic or the Hydromatic.

Glassware is inspected, wrapped with aluminum foil and brown paper or inverted in a tray lined with paper.

Sterilization is by Dry Wall method—356° F. (180° C.) for 3 hours.

*Can Washer*—100 liter stainless steel cans

This washer is divided into two units. One side for washing is equipped with a spray nozzle, steam coil, and a circulating pump; the other side for rinsing is equipped with hot tap water and deionized distilled water controlled by quick opening valves.

Cans are stripped of all rubber tubing, lids removed and placed in large steam coil equipped tub for boiling.

Can is placed over the jet on the washing side of the unit. Boiling water containing 1% Aura solution is sprayed for 5 minutes into the tank. Pump is turned off and can is then placed on the rinsing side of the washer where it receives a 5 minute hot tap water rinse followed by a 3 minute deionized distilled water rinse. Can is removed, inspected, and covered by paper until assembled.

Lids for cans are boiled for 10 minutes in tap water, rinsed and flushed with deionized distilled water for 3 minutes.

50 ml. of deionized water is put in each can prior to sterilization. Inlet and outlet lines are wrapped with gauze and paper. The entire top is covered with a canvas bag. Sterilization is by autoclave—250° F. (122° C.) for 30 minutes.

*Tumbler Washer*—Rubber Stoppers
Machine Assemblies
Rubber Tubing
Rubber Gaskets

Stoppers are placed in tumbling barrel containing tap water with 1% Aura. Water is boiled and stoppers tumbled for 20 minutes. Stoppers are rinsed in tap water twice for 5 minutes, twice in distilled water for 5 minutes, and once in deionized distilled water for 3 minutes.

Stoppers are inspected and packed in either stainless steel cans or wrapped in brown paper.

Rubber tubing, machine assemblies, and rubber gaskets are placed in tumbling barrel and covered with distilled water, boiled and tumbled for 20 minutes. Barrel is emptied and equipment is rinsed in distilled water for 5 minutes. All machines and tubing are flushed with deionized distilled water immediately before preparation for sterilization. Excessive water is drained from tubing but not dried.

Machine ends are wrapped in gauze and paper. Inlet and outlet lines used within the bottle are placed in paper envelopes and canvas bags.

Rubber stoppers and machine assemblies are sterilized by autoclave at 250° F. (122° C.) for 30 minutes. All stoppers are dried overnight. Stoppers for 5 liter Povitsky bottles are held in an incubator until used.

*Technicon Washer*—Serological Pipettes
Volumetric Pipettes
Capillary Pipettes
Drawing-off Rods

All of the above items are soaked in a 1% solution of Aura for a minimum period of 8 hours. Cotton plugs are blown out by the use of water pressure. Pipettes are washed by hand in a 1% solution of Duponol C. Duponol is drained off and pipettes are rinsed in tap water until all suds have disappeared. Pipettes and rods are then placed in Technicon baskets and rinsed in the Technicon for 10 minutes with deionized distilled water. Basket is then removed from the Technicon and excess water is drained from pipettes before being placed in oven for drying. When pipettes are completely dry they are removed from the oven, cooled, inspected, plugged with cotton, inserted in can or envelope as required, and put in tray for sterilization.

This operation is now under study and the indications are that it can be improved in quality and speed by an adapter for the Turbomatic, using high pressure washing and rinsing.

Sterilization is by Electric Dry Wall method, 3 hours at 356° F. (180° C.).

*Hand Washing*—Waring Blendors
Trypsinizers
Syringes (automatic)
Dispensing Bells
Graduates

All items being hand washed are soaked in a 1% solution of Aura detergent overnight.

Waring Blendors, trypsinizers, and automatic syringes are completely disassembled. All pieces are brushed in a 1% solution of Aura, brushed in a 1% solution of Duponol C, rinsed twice in tap

water, twice in distilled water and finally with deionized distilled water. All pieces are placed in trays and dried in oven.

Before assembling the Blendors, trypsinizers, or syringes, all parts must be thoroughly inspected. Gaskets must be inspected for cracks or breaks. The revolving blade mechanism is checked for freedom of motion.

Units wrapped in a double thickness of brown paper. Sterilization is by autoclave 250° F. (122° C.) for 30 minutes.

Graduates are wrapped with aluminum foil and brown paper. Sterilization is by Electric Dry Wall—356° F. (180° C.) for 3 hours.

*Stainless Steel Tanks*—240 liter Regular
240 liter Rod
240 liter Mixing
700 liter Mixing

Immediately after tanks have been decontaminated they are disassembled, filled with hot tap water containing 8 ounces of Aura, and soaked for a minimum of 1 hour. While tank is being filled the inside of the cans are scrubbed with a cloth swab.

Water is removed and can inverted, placed over a rinsing device consisting of a hot tap water line and a deionized distilled water line joined at floor level. Valves provide independent operation of each line. Water is ejected, by use of house pressure, through a spray nozzle. Cans are rinsed by hot tap water for 10 minutes followed by a 3 minute rinse of deionized distilled water. When rinse is completed cans are turned upright and covered. Lids, tubing assemblies, and gaskets are boiled and rinsed with deionized water.

Inlet, outlet, and air filter lines are equipped with red rubber tubing and double air filters. Air filters on inlet and outlet lines are removable for the insertion of a 2, 4, 6, or 8 way connectors prepared as single units. All air filters are wrapped in double envelopes.

Sample lines are equipped with a 24″ piece of gum tubing with a metal connector on the end. Four inches of the sample line end is wrapped in gauze and paper secured by string.

On mixing tanks the propellor shaft, extending above the lid, is wrapped with gauze and paper.

The entire lid is encased in a canvas bag secured by heavy twine. Sterilization is by autoclaving at 250° F. (122° C.) for a period of 1 hour.

**Special Treatments**

The foregoing discussion covers most of the production glassware washing operations that are handled routinely in this area. As we are all aware, there are certain situations that preclude the immediate washing of glassware after sterilization. The cleaning of glassware that has been used and sterilized several times and allowed to become dried after sterilization is a rather difficult task and requires special consideration as far as the washing operation is concerned. We have found that the only successful method of washing heavily soiled glassware is through a soaking process. In order to soak glassware properly it is necessary that the soaking tank be deep enough to submerge the tallest bottle. This tank should be equipped with a steam coil. The soaking solution should be composed of soft water with ½ ounce of good detergent per gallon. The glassware must be placed in the tank in an upright position, making certain that all bottles are filled with the solution. The solution is brought to a boil and held for 1½ hours. Our best results have been obtained in allowing the glassware to remain in the solution overnight, cooling down gradually. The contents of the tank can now be removed and washed by hand or on a bottle washing machine.

In our experience, Blake bottles containing chocolate agar are about the most difficult to get clean, due to the small neck of the bottle, which makes it difficult to remove the sterilized blood. These bottles can be cleaned successfully by the Better Built "Hydro" Washer if a good detergent is used.

The cleaning of glassware used in conducting very sensitive tests is best accomplished by using Dichromate Cleaning Solution. Although I am sure you are familiar with this formula, we included our method for purposes of completeness.

| | |
|---|---|
| Potassium Dichromate | 1000 grams |
| Sulfuric Acid | 2.5 liters |
| Tap Water | 6.5 liters |

The Dichromate must be dissolved in hot water then allowed to cool to 50° C. The Sulfuric Acid is added slowly while stirring the solution. Soaking glassware overnight in this solution and rinsing with tap water plus a final distilled water rinse will yield a perfectly clean container.

Our Safety Engineer, Mr. Jack Gausch, asked me to remind you of the inherent dangers of making and using this cleaning solution. Gloves and goggles should be used for protection of the personnel.

## Final Market Container Glassware

The equipment we use to wash market container glassware is designed to handle containers in volume quantities and to expose each piece to a pre-determined washing cycle. In all, five separate machines are used to cleanse the various types and sizes of containers into which our products are filled. Each machine is designed to wash a specific range of sizes or type of container.

The Perfektum Ampwash Model W-700 washes bottles from 5 ml. to 20 ml. at a speed of approximately 100 bottles per minute.

For bottles from 1 ml. to 3 ml. and ampuls from 5 ml. to 20 ml., we use the Perfektum Ampwash Model W-200, which operates at 60 containers per minute.

The Perfektum Ampul Washer Model GW-12 prepares 1 ml. and 2 ml. ampuls. This machine washes one gross of ampuls per one minute cycle.

Two rotary washers handle the larger containers, one a Perfektum Model on which we wash 50 ml. ampuls; the other a Better Built Rotary Washer on which 30 ml. to 850 ml. bottles are processed.

The washing cycle is the same on all machines, and consists of a jet of air to remove loose particles in the containers, then a shock treatment which is produced by injecting steam and following this, a rinse of cold distilled water. This shock treatment of steam is repeated and then the container is rinsed with hot distilled water. Air is now injected to remove the excess water and the container is removed from the machine. The outside of the container is washed with hot distilled water while the container is passing through the various stages of the inside washing cycle.

All of the water used to cleanse market containers is pyrogen-free distilled water. This is accomplished by storing the distilled water at 180° F. until used. Cold pyrogen-free distilled water is produced by passing the hot distilled water through a heat exchanger immediately before use. The steam used in our equipment is manufactured from pyrogen-free distilled water. In no case is a detergent or other agent, except filtered steam, air and distilled water, used in preparing new market containers for use.

## Control of Linters

It is important that the stainless steel boxes used in packing finished glassware are thoroughly cleaned and handled on a separate

machine to eliminate the possibility of having any residual cotton fibers attach themselves to these containers from water in which cotton linters or other fibers may have become entrained. We believe that this area devoted to packing should be isolated from any cotton or gauze handling rooms which might be in the same general area.

### Personnel and Credits

Of course, all of the equipment, facilities, controls, etc., in the world will not result in a good operation unless the people responsible for this important job are properly trained and impressed with the importance of their job. We are not putting enough emphasis on this part of our job. We spend hours with the salesman telling us about a super deluxe detergent and, while this is important, it is more important to spend some time with our people associated with this operation, praising their efforts in supplying glassware. A few minutes with sincere interest in his or her problems and a sympathetic understanding with the appropriate appreciation of the job they are doing will bring about glassware washing miracles. It is a heck of a job under the best of conditions and its important contribution to your over-all operations should not be under-estimated.

The operations at Merck Sharp & Dohme are possible only because we operate as a team. This presentation was made possible by the efforts of Mr. Walter L. Smith, Mr. Larry Cunningham, Mr. Roy Greene, and Mr. Edward Lewis, all staff members of the Merck Sharp & Dohme Biological Laboratories.

I wish to thank the Committee for this opportunity of discussing some of our methods with you and hope that some of our thoughts on this subject may be of some assistance.

# AN EVALUATION OF THE ANTIHISTAMINIC ACTIVITY OF A NEW SERIES OF CHALCONE DERIVATIVES[1]

By G. Victor Rossi and Joseph D. Avellino

CLARK (1) reported in 1953 that adrenergic blocking activity, a property previously discovered in many classes of organic compounds, was also characteristic of certain hydroxychalcones. He postulated that the hydroxychalcones act by blocking the biosynthesis of norepinephrine, the adrenergic neurohumoral transmitter, presumably by inhibiting the decarboxylation of dihydroxyphenylalanine. On this basis, Packman (2) synthesized a series of chalcone derivatives primarily as potential adrenergic blocking agents.[2] However, certain of the structural features of these chalcones warranted investigation of their antihistaminic activity. Notably the groups joined by ether linkage to the chalcone nucleus are disubstituted alkylamino moieties, forming a structural class to which many potent antihistamines belong. The terminal nitrogen is tertiary, with some of the componuds possessing the N-dimethyl group generally found to be optimal for antihistaminic activity.

## Materials and Methods

Of the original series of compounds synthesized by Packman (2), those listed in Table 1 were available for pharmacologic evaluation.[3] Henceforth in this report the compounds will be referred to by the code letter assigned for the investigation.

*In vitro*—Preliminary screening procedures were performed on isolated guinea pig ileum by a modification of the Magnus method. Segments (2 cm.) of the distal ileum were removed from freshly

1. Received from the LaWall Memorial Laboratory of Pharmacology and Biochemistry, Philadelphia College of Pharmacy and Science, Philadelphia, Pennsylvania.

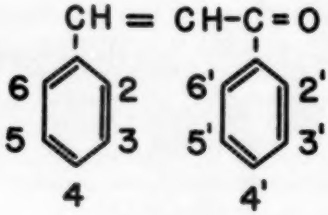
2. The cardiovascular activity of these chalcones will form the basis of a subsequent report.

3. The chalcones employed in this study were generously supplied by Dr. Nathan Rubin, Department of Chemistry, Philadelphia College of Pharmacy and Science, and Dr. Albert Packman, Department of Organic Chemistry, National Drug Company Research Laboratories, Philadelphia, Pennsylvania.

killed adult male guinea pigs of the English smooth hair variety (300 to 500 Gm. body weight), which had been fasted for 24 hours prior to the experimentation. The test strips were suspended in aerated Tyrode's solution maintained at 37.5 ± 0.5° C., and 30 minutes were allowed for equilibration with the new environment. An amount of histamine necessary to elicit a submaximal contraction of 30 to 50 mm. was empirically determined for each muscle strip. Usually 1 to

---

TABLE 1



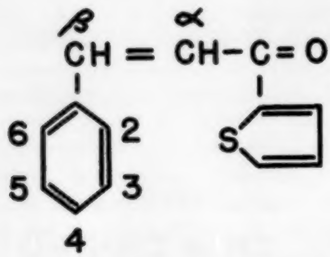

CHALCONE

The method of numbering the substituted chalcones is based on the system used in Chemical Abstracts.

| Code Letter | Group Substituted on Chalcone | Position on Chalcone |
|---|---|---|
| A | $(CH_3)_2NCH_2CH_2O\text{-}$ | 2 |
| C | $(C_2H_5)_2NCH_2CH_2O\text{-}$ | 2 |
| D | $(C_2H_5)_2NCH_2CH_2CH_2O\text{-}$ | 4 |
| E | $(CH_3)_2NCH_2CH_2O\text{-}$ | 4 (citrate) |
| F | $(CH_3)_2NCH_2CH_2CH_2O\text{-}$ | 4 |
| G | $(C_2H_5)_2NCH_2CH_2O\text{-}$ | 4′ |
| H | $(CH_3)_2NCH_2CH_2CH_2O\text{-}$ | 4′ |
| I | $(C_2H_5)_2NCH_2CH_2O\text{-}$ | 2′ |
| J | $(CH_3)_2NCH_2CH_2O\text{-}$ | 4 (HCl) |
| K | $(CH_3)_2NCH_2CH_2O\text{-}$ | 4′ |
| M | $(CH_3\text{-}\underset{\substack{\vert \\ CH_3}}{CH}\text{-})_2NCH_2CH_2O\text{-}$ | 4 |
| N | $(C_2H_5)_2NCH_2CH_2O\text{-}$ | 4 |

TABLE 1 (Cont.)

ADDITIONAL COMPOUNDS



alpha-(2-thenoyl)-beta-phenylethylene

| Code Letter | Group Substituted on Benzene Ring | Position on Benzene Ring |
|---|---|---|
| B | $(CH_3)_2NCH_2CH_2O-$ | 4 |
| L | $(C_2H_5)_2NCH_2CH_2O-$ | 4 |

3 mcg. of histamine (calculated as the free base) per 100 ml. of tissue bath were sufficient. After the histamine had remained in contact with the muscle strip for exactly 1 minute, the bath was drained and refilled with fresh Tyrode's solution twice during a 5 minute interval. This procedure was repeated 3 times with the same concentration of histamine; the mean contraction served as the control response.

The compound being evaluated was then added in an amount calculated to provide a concentration of 100 mcg. per 100 ml. of bath. This relatively high concentration of chalcone was chosen to enable detection of even minimal *in vitro* antihistaminic activity. After the compound had remained in contact with the tissue for 3 minutes, without washing, the standard amount of histamine was again added to obtain the test response. The tissue was alternately washed with Tyrode's solution and exposed to histamine until the contractions returned to the control level.

Inasmuch as many antihistamines also exhibit anticholinergic and musculotropic spasmolytic properties, it was considered desirable

to determine the protection provided by these chalcones against the spasmogenic effects of acetylcholine and barium chloride. The procedure described above was followed with minor modifications; the concentration of reagents used are given in Table 2.

The three chalcones exhibiting the greatest antihistaminic activity on the basis of the technique employed were re-examined on isolated guinea pig small intestine according to a somewhat more quantitative procedure. An amount of histamine (10 mcg., calculated as the free base, per 100 ml. of bath) sufficient to induce maximal contractions of the ileum was added to the bath to determine the control response. The tissue was washed twice with Tyrode's solution during an interval of 10 minutes, and then the test response was obtained by adding the control concentration of histamine after exposure of the muscle strip for 3 minutes to graded concentrations of thes test compound. The concentrations of the chalcones employed were 0.1, 1.0, 10 and 100 mcg. per 100 ml. of tissue bath. Diphenhydramine hydrochloride (Benadryl), representative of an antihistamine having the alkylamino ether structure, was used in the same concentrations for comparison.

*In vivo*—The compounds of this series that manifested the greatest antihistaminic activity on the basis of the *in vitro* procedures were tested for their ability to inhibit the characteristic, rapid, transient drop in blood pressure elicited by the intravenous administration of histamine. Female cats (1.5 to 2 Kg.), fasted for 12 hours before the experimentation, were anesthetized with 35 mg./Kg. of sodium pentobarbital injected intraperitoneally. Blood pressure was recorded directly by means of a mercury manometer joined to a cannulated femoral artery with polyethylene tubing.

A dose of 1 mcg. of histamine (calculated as the free base) per Kg. of body weight was injected into a femoral vein to obtain a control depressor response. Allowing sufficient time between injections for complete normalization of blood pressure, the same dose was repeated for a total of 3 injections during a 15 minute period. The chalcone being tested was then administered intravenously in a dose of 1 mg./Kg., and after a 10 minute interval, the standard dose of histamine was repeated. This same procedure was also followed for 2, 3, and 4 mg./Kg. doses of the chalcone. The inhibition of the histamine depressor response provided by 4 mg./Kg. of diphenhydramine hydrochloride served as a basis for comparison.

## TABLE 2

AVERAGE PER CENT INHIBITION OF THE CONTRACTILE RESPONSE TO HISTAMINE, ACETYLCHOLINE AND BARIUM CHLORIDE IN THE ISOLATED GUINEA PIG ILEUM BY GRADED DOSES OF THE MOST ACTIVE CHALCONES

HISTAMINE

10 mcg./100 ml.

| Compound | Concentration of Antagonist in mg./100 ml. 0.0001 | 0.001 | 0.01 | 0.1 |
|---|---|---|---|---|
| A | 0* | 0 | 0 | 10 |
| C | 0 | 0 | 8 | 18 |
| D | 0 | 0 | 0 | 14 |
| Diphenhydramine | 0 | 73 | 85 | — |

ACETYLCHOLINE

100 mcg./100 ml.

| Compound | Concentration of Antagonist in mg./100 ml. 0.01 | 0.1 | 1.0 |
|---|---|---|---|
| A | 0 | 0 | 54 |
| C | 0 | 58 | 97 |
| D | 0 | 60 | 96 |
| Diphenhydramine | 0 | 70 | 100 |
| Atropine | 100 | — | — |

BARIUM CHLORIDE

500 mcg./100 ml.

| Compound | Concentration of Antagonist in mg./100 ml. 0.5 | 5.0 | 50.0 |
|---|---|---|---|
| A | 66 | 97 | 100 |
| C | 50 | 100 | 100 |
| D | 66 | 98 | 100 |
| Diphenhydramine | 56 | 100 | 100 |
| Papaverine | 10 | 95 | 100 |

* Each figure represents the average of determinations made on three isolated muscle strips.

## Results and Discussion

On the basis of the preliminary pharmacologic evaluation of the series of substituted chalcones synthesized by Packman (2), the three derivatives manifesting the greatest antihistaminic activity *in vitro* were compounds A, C and D. The criterion for their selection for further study was a minimum of 50% inhibition (mean of three successive determinations) of the contractile response of isolated guinea pig ileum to submaximal concentrations of histamine. In view of the relatively high ratio of chalcone to histamine, approximately 100 to 1 respectively, a degree of inhibition less than 50% was considered insignificant for the purposes of this study (data obtained with the less active members of the group are not tabulated in this report).

The availability of a series of structurally related compounds with which to investigate a specific pharmacologic property affords the opportunity to make certain observations regarding the relationship between structure and activity. In this series, substitution at the 2 (ortho) position appears to provide maximal antihistaminic activity; substitution at the 4 (para) position also results in activity, but of a lesser degree. With few exceptions, substitution at the 2′ or 4′ positions, regardless of the nature of the side-chain, results in compounds with minimal antihistaminic potency. The influence of the diethylaminoethoxy group at the 2 (ortho) position of chalcone is demonstrated by compound C, found to be the most effective antihistaminic of this series according to both *in vitro* and *in vivo* tests. Although contrary to what has been generally observed with other classes of antihistaminic compounds, in this series, the N-diethyl grouping offers greater activity than the N-dimethyl grouping. Lengthening the side chain from diethylaminoethoxy (compound C) to diethylaminopropoxy (compound D) did not materially reduce antihistaminic activity, however conversion to dimethylaminopropoxy decreased (compound H) or practically abolished (compound F) activity. Replacement of benzene by a thenoyl group on the alpha carbon of chalcone produced compounds (B and L) with negligible antihistaminic effectiveness.

It may be observed from the data presented in Table 2 that a concentration of 2-(2-diethylaminoethoxy) chalcone citrate (compound C) 100 times greater than diphenhydramine was required to provide one-fourth the degree of inhibition of the maximal contractile response to histamine obtained with the latter compound. On this

basis, diphenhydramine is approximately 400 times more effective as an antihistamine than the most active chalcone, therefore it may be concluded that this series of compounds is devoid of significant *in vitro* antihistaminic activity.

In order to substantiate this conclusion, it was considered desirable to reexamine these compounds utilizing an *in vivo* procedure. The degree of inhibition of the depressor response to intravenous histamine in anesthetized cats obtained with various doses of the three most effective chalcones (compounds A, C, and D) is compared with diphenhydramine in Table 3. These data indicate compound C to be significantly less active than diphenhydramine *in vivo*. It is generally recognized, however, that this procedure frequently does not provide an adequate measure of the potency differences between antihistaminic substances.

The degree of antihistaminic specificity has been expressed as the ratio of the amount of drug required to antagonize acetylcholine or barium chloride to that required to inhibit histamine (3). The value of this ratio for diphenhydramine is approximately 400 times greater than the corresponding value for compound C. Thus it is evident that both antihistaminic potency and antihistaminic specificity of diphenhydramine are considerably greater than those of 2-(2-diethylaminoethoxy) chalcone citrate, the most active of the series of chalcones investigated.

TABLE 3

AVERAGE PER CENT INHIBITION OF THE DEPRESSOR RESPONSE TO HISTAMINE IN THE ANESTHETIZED CAT BY GRADED DOSES OF THE MOST ACTIVE CHALCONES

HISTAMINE

1 mcg./Kg. intravenously

| | Dose of Antagonist in mg./Kg. intravenously | | | |
|---|---|---|---|---|
| Compound | 1 | 2 | 3 | 4 |
| A | 0* | 0 | 0 | 10 |
| C | 0 | 11 | 23 | 38 |
| D | 0 | 0 | 0 | 0 |
| Diphenhydramine | — | — | — | 68 |

* Each figure represents the average of determinations made on two or more animals.

BIBLIOGRAPHY

(1) Clark, W. G., *Chem. Eng. News 31:*1401 (1953).

(2) Packman, A. M., Doctor of Science Thesis, Department of Chemistry, Philadelphia College of Pharmacy and Science, 1956.

(3) Loew, E. R., *Ann. N. Y. Acad. Sci. 50:*1142 (1950).

# AN IMPROVED FORMULA FOR PHENOBARBITAL ELIXIR AND PENTOBARBITAL ELIXIR *

By Martin Barr and Linwood F. Tice

STUDIES have been carried out by the authors in order to determine in what preparations Sorbitol Solution, N. F. X, may be used with advantage. This paper reports on the use of this solution in the formulation of phenobarbital and pentobarbital elixirs.

Sorbitol Solution is officially recognized in the Tenth Edition of the *National Formulary* (1). It is used increasingly in the formulation of pharmaceutical preparations because of some of its properties. Among these are its sweet taste, humectant action, chemical inertness, relatively high viscosity, uniformity, availability, and relatively low cost.

## Experimental Procedure

### *Solubility Studies*

Phenobarbital Elixir, U. S. P. XV, (2) contains 0.4% phenobarbital as the active ingredient. Pentobarbital Elixir, N. F. X, (3) contains 0.4% pentobarbital sodium which is converted to the keto (acidic) form of pentobarbital by the action of the diluted hydrochloric acid specified in the official formula.

In this study the possible use of a solvent containing sorbitol rather than glycerin was investigated.

Solubility studies were conducted in order to obtain a vehicle having satisfactory solvent power for both phenobarbital and pentobarbital. The solvents included in the study were alcohol; mixtures of alcohol and propylene glycol; and mixtures of alcohol, propylene glycol, and Sorbitol Solution N. F.[1]. Purified Water was used as the diluent.

The solubilities of 0.4% phenobarbital and pentobarbital, the latter formed by the addition of 0.6% diluted hydrochloric acid to 0.4% pentobarbital sodium, were determined in various solvent mixtures at

---

* From the Department of Pharmacy, Philadelphia College of Pharmacy and Science. Work supported by research grant from Atlas Powder Company, Wilmington, Del.

[1] Sorbo ®, Atlas Powder Company, Wilmington, Delaware.

25° C. and 4° C. All solutions were observed for a period of thirty days for evidence of precipitation. The results are tabulated in Tables I-III.

The data indicate that alcohol alone, even at a concentration of 30%, is not capable of solubilizing 0.4% phenobarbital or pentobarbital at 4° C. In Table II, it is seen that either an aqueous solution containing 15% alcohol and 30% propylene glycol or one containing 20% alcohol and 20% propylene glycol mixture is required to solubilize 0.4% phenobarbital or pentobarbital. A mixture of 12.5% alcohol and 30% propylene glycol also solubilized the pentobarbital. It was obvious that such concentrations of propylene gly ol could not be used in elixirs without influencing the taste unfavorably.

It is seen in Table III that the addition of Sorbitol Solution to alcohol-propylene glycol combinations increases the solubility of phenobarbital and pentobarbital. It was found that the addition of 35 parts Sorbitol Solution N. F. to 20 parts of alcohol and 10 parts propylene glycol in the formula brought about the solubilization of 0.4% phenobarbital at 4° C., and that the addition of 25 parts Sorbitol Solution to 20 parts alcohol and 10 parts propylene glycol in the formula resulted in the solubilization of 0.4% pentobarbital at the same temperature. It was, therefore, decided to use those combinations as the

TABLE I

Solubility of Phenobarbital and Pentobarbital in Alcohol

| | Phenobarbital[a] | | Pentobarbital[b] | |
|---|---|---|---|---|
| % v/v Alcohol | 25° C. | 4° C. | 25° C. | 4° C. |
| 5 | ppt. | ppt. | ppt. | ppt. |
| 10 | ppt. | ppt. | ppt. | ppt. |
| 15 | ppt. | ppt. | ppt. | ppt. |
| 20 | ppt. | ppt. | ppt. | ppt. |
| 25 | ppt. | ppt. | no ppt. | ppt. |
| 30 | no ppt. | ppt. | no ppt. | ppt. |

[a] 0.4% phenobarbital.

[b] Pentobarbital formed from 0.4% pentobarbital sodium by 0.6% diluted hydrochloric acid.

solvents for the phenobarbital and pentobarbital in the further studies on the development of formulas for their respective elixirs.

*Flavoring Agent Studies*

*Phenobarbital Elixir*—At this stage of the study, the specifications for a formula for an unflavored phenobarbital elixir were as follows:

| | |
|---|---|
| Phenobarbital | 4 Gm. |
| Alcohol | 200 ml. |
| Propylene Glycol | 100 ml. |
| Sorbitol Solution | 350 ml. |
| Purified Water q.s. ad. | 1000 ml. |

It was decided to use orange oil as the flavoring agent in the elixir. This oil is also the flavoring agent in Phenobarbital Elixir, U. S. P. XV, (2).

One of the problems encountered in preparing most elixirs is the difficulty and time consumed in filtration. This problem arises for several reasons. The flavoring agents used in elixirs usually contain ingredients, such as volatile oils, which are soluble only in high concentrations of alcohol. Since most elixirs have a relatively low alcohol concentration, these constituents are thrown out of solution to some extent and the finished product must be filtered. Since the elixirs also usually contain a high concentration of sugar, filtration is often quite difficult.

It was found that, by increasing the amount of Sorbitol Solution N. F. in the formula for phenobarbital elixir the taste of the preparation was improved due to the additional sweetness of the polyol solution. It was also possible to prepare an elixir which did not require filtration but still containing a sufficient amount of orange oil as a flavoring agent. The data leading to this conclusion are listed in Table IV.

It may be noted from Table IV that, by increasing the amount of Sorbitol Solution N. F. to 60 parts, 0.025% orange oil may be added to the elixir with complete solution at 4° C. This is probably explained by the fact that by increasing the amount of Sorbitol Solution in the formula, the concentration of water is reduced and, in this way, the solubility of the orange oil is increased.

TABLE II

SOLUBILITY OF PHENOBARBITAL AND PENTOBARBITAL IN ALCOHOL-PROPYLENE GLYCOL-PURIFIED WATER MIXTURES

| % v/v Alcohol | % v/v Propylene Glycol | Phenobarbital[a] 25° C. | Phenobarbital[a] 4° C. | Pentobarbital[b] 25° C. | Pentobarbital[b] 4° C. |
|---|---|---|---|---|---|
| 12.5 | 5 | ppt. | ppt. | ppt. | ppt. |
| 12.5 | 10 | ppt. | ppt. | no ppt. | ppt. |
| 12.5 | 15 | ppt. | ppt. | no ppt. | ppt. |
| 12.5 | 20 | ppt. | ppt. | no ppt. | ppt. |
| 12.5 | 25 | no ppt. | ppt. | no ppt. | ppt. |
| 12.5 | 30 | no ppt. | ppt. | no ppt. | no ppt. |
| 15.0 | 5 | ppt. | ppt. | ppt. | ppt. |
| 15.0 | 10 | ppt. | ppt. | no ppt. | ppt. |
| 15.0 | 15 | ppt. | ppt. | no ppt. | ppt. |
| 15.0 | 20 | no ppt. | ppt. | no ppt. | ppt. |
| 15.0 | 25 | no ppt. | ppt. | no ppt. | ppt. |
| 15.0 | 30 | no ppt. | no ppt. | no ppt. | no ppt. |
| 20.0 | 5 | no ppt. | ppt. | no ppt. | ppt. |
| 20.0 | 10 | no ppt. | ppt. | no ppt | ppt. |
| 20.0 | 15 | no ppt. | ppt. | no ppt. | ppt. |
| 20.0 | 20 | no ppt. | no ppt. | no ppt. | no ppt. |
| 20.0 | 25 | no ppt. | no ppt. | no ppt. | no ppt. |
| 20.0 | 30 | no ppt. | no ppt. | no ppt. | no ppt. |

[a] 0.4% phenobarbital.

[b] Pentobarbital formed from 0.4% pentobarbital sodium by 0.6% diluted hydrochloric acid.

*Pentobarbital Elixir*—At this stage of the work, the specifications for a formula for an unflavored pentobarbital elixir were as follows:

| | |
|---|---|
| Pentobarbital Sodium | 4 Gm. |
| Alcohol | 200 ml. |
| Propylene Glycol | 100 ml. |
| Diluted Hydrochloric Acid | 6 ml. |
| Sorbitol Solution | 250 ml. |
| Purified Water q.s. ad. | 1000 ml. |

It was decided to employ 3% Sweet Orange Peel Tincture, U. S. P. XV, (4) as the flavoring agent. This tincture is used and in this same concentration in the N. F. X elixir (3).

Similar to the experimental findings in the work on phenobarbital elixir, it was found that a better tasting elixir and one not requiring filtration could be prepared by increasing the amount of sorbitol solution used. The data which reveal the effect of the concentration of sorbitol solution on the need for filtration of the pentobarbital elixir are listed in Table V.

It is noted from Table V that, by increasing the amount of Sorbitol Solution to 60 parts, 3% sweet orange peel tincture may be used in the elixir with complete solution at 4° C. It should be observed that a clear elixir may also be formed at 25° C. using 45 parts Sorbitol Solution, but this preparation does become cloudy at 4° C.

## Discussion

Based on the research thus far described, the following formula was decided upon for phenobarbital elixir:

PHENOBARBITAL ELIXIR

| | | |
|---|---|---|
| Phenobarbital | 4 | Gm. |
| Orange Oil | 0.25 | ml. |
| Amaranth Solution | 10 | ml. |
| Alcohol | 200 | ml. |
| Propylene Glycol | 100 | ml. |
| Sorbitol Solution | 600 | ml. |
| Purified Water q.s. ad. | 1000 | ml. |

Dissolve the phenobarbital in the alcohol, then add the propylene glycol, orange oil, sorbitol solution, and amaranth solution. Mix thoroughly, and add sufficient purified water to make the product measure 1000 ml. Mix well.

TABLE III

SOLUBILITY OF PHENOBARBITAL AND PENTOBARBITAL IN ALCOHOL-PROPYLENE GLYCOL-SORBITOL SOLUTION-PURIFIED WATER MIXTURES

| % v/v Alcohol | % v/v Propylene Glycol | % v/v Sorbitol Solution N. F. | Phenobarbital[a] 25° C. | Phenobarbital[a] 4° C. | Pentobarbital[b] 25° C. | Pentobarbital[b] 4° C. |
|---|---|---|---|---|---|---|
| 15 | 5 | 25 | ppt. | ppt. | ppt. | ppt. |
| 15 | 5 | 35 | ppt. | ppt. | ppt. | ppt. |
| 15 | 5 | 45 | ppt. | ppt. | ppt. | ppt. |
| 15 | 5 | 60 | ppt. | ppt. | no ppt. | ppt. |
| 15 | 10 | 25 | no ppt. | ppt. | no ppt. | ppt. |
| 15 | 10 | 35 | no ppt. | ppt. | no ppt. | ppt. |
| 15 | 10 | 45 | no ppt. | ppt. | no ppt. | no ppt. |
| 15 | 10 | 60 | no ppt. | no ppt. | no ppt. | no ppt. |
| 20 | 5 | 25 | ppt. | ppt. | no ppt. | ppt. |
| 20 | 5 | 35 | no ppt. | ppt. | no ppt. | ppt. |
| 20 | 5 | 45 | no ppt. | ppt. | no ppt. | ppt. |
| 20 | 5 | 60 | no ppt. | no ppt. | no ppt. | no ppt. |
| 20 | 10 | 25 | no ppt. | ppt. | no ppt. | no ppt. |
| 20 | 10 | 35 | no ppt. | no ppt. | no ppt. | no ppt. |
| 20 | 10 | 45 | no ppt. | no ppt. | no ppt. | no ppt. |
| 20 | 10 | 60 | no ppt. | no ppt. | no ppt. | no ppt. |

[a] 0.4% phenobarbital.

[b] Pentobarbital formed from 0.4% pentobarbital sodium by 0.6% diluted hydrochloric acid.

*Description*

The pH of this elixir is 6.2-6.4 which is similar to that of the U. S. P. product. It is a brilliant red in color and cannot be distinguished in this respect from the official elixir.

The flavoring oil, orange oil, is completely soluble in the product. Therefore, there is no need for filtration of the elixir other than to remove foreign matter. In order to eliminate the usual required filtration of the elixir, it was found necessary to reduce the concentration of orange oil from 0.075% (the concentration in the official elixir) to 0.025%. At this concentration, no turbidity was observed in the elixir when stored at 25° C. and 4° C. Although as much as 0.05% orange oil in the elixir will not produce turbidity at 25° C., some turbidity does appear almost immediately at 4° C. Therefore, in order to insure clarity without filtration, only 0.025% orange oil is recommended.

Actually, the orange oil (0.075%) in the official formula for Phenobarbital Elixir is excessive. It would not be surprising if the amount of oil in the filtered elixir approaches the level of 0.025%. It should also be noted that Phenobarbital Elixir, U. S. P. XV, becomes turbid when stored at 4° C. due to the lower solubility of the orange oil at this temperature. In this respect, the newly formulated elixir has an advantage.

*Bacteriological Testing*

Bacteriological testing indicated no need for preservation. This was not unexpected since the elixir contains 20% alcohol and 10% propylene glycol, both of which are inhibitory to the growth of microorganisms.

*Taste Panel Studies*

Taste panel comparisons on the newly formulated phenobarbital elixir and the official elixir were carried out using two panels of thirty members each. An analysis of the taste panel comparisons revealed no significant preference for either of the elixirs. Many panelists could not differentiate between them. It is the opinion of the authors that the bitter taste of the phenobarbital completely masks whatever taste difference there may be between the vehicle in the modified formula and that in the official formula.

*Cost Analysis*

The cost of the suggested formula for phenobarbital elixir was calculated and compared to that for the official elixir. It was found that the cost * of the suggested formula is $0.08 per liter less than that for Phenobarbital Elixir, U. S. P. XV.

* * * * *

TABLE IV

EFFECT OF CONCENTRATION OF SORBITOL SOLUTION ON THE CONCENTRATION OF ORANGE OIL WHICH COULD BE ADDED TO PREPARE A PHENOBARBITAL ELIXIR NOT REQUIRING FILTRATION [a]

| % v/v Sorbitol Solution N. F. | % v/v Orange Oil | 25° C. | 4° C. |
|---|---|---|---|
| 35 | 0.075 | Turbid | Turbid |
| 35 | 0.050 | Turbid | Turbid |
| 35 | 0.040 | Turbid | Turbid |
| 35 | 0.025 | Turbid | Turbid |
| 45 | 0.075 | Turbid | Turbid |
| 45 | 0.050 | Turbid | Turbid |
| 45 | 0.040 | Turbid | Turbid |
| 45 | 0.025 | Turbid | Turbid |
| 60 | 0.075 | Turbid | Turbid |
| 60 | 0.050 | Turbid | Turbid |
| 60 | 0.040 | Clear | Turbid |
| 60 | 0.025 | Clear | Clear |

* Based on price quotations given in Oil, Paint and Drug Reporter, Nov. 1956.

[a] Other ingredients of elixir are 0.4% phenobarbital, 20% alcohol, 10% propylene glycol, and purified water, q.s.

The following formula was decided upon for pentobarbital elixir:

PENTOBARBITAL ELIXIR

| | |
|---|---|
| Pentobarbital Sodium | 4 Gm. |
| Sweet Orange Peel Tincture | 30 ml. |
| Alcohol | 200 ml |
| Propylene Glycol | 100 ml. |
| Sorbitol Solution | 600 ml. |
| Diluted Hydrochloric Acid | 6 ml. |
| Caramel | 2 Gm. |
| Purified Water q.s. ad. | 1000 ml. |

Dissolve the pentobarbital sodium in 60 ml. of purified water; then, add the sorbitol solution, alcohol, propylene glycol, sweet orange peel tincture, and caramel. Mix thoroughly, and add the diluted hydrochloric acid and sufficient purified water to make the product measure 1000 ml. Mix well.

TABLE V

EFFECT OF CONCENTRATION OF SORBITOL SOLUTION ON THE NEED FOR FILTRATION OF PENTOBARBITAL ELIXIR CONTAINING 3% SWEET ORANGE PEEL TINCTURE [a]

| % v/v Sorbitol Solution N. F. | 25° C. | 4° C. |
|---|---|---|
| 25 | Turbid | Turbid |
| 35 | Turbid | Turbid |
| 45 | Clear | Turbid |
| 60 | Clear | Clear |

[a] Other ingredients of elixir are 0.4% pentobarbital sodium, 20% alcohol, 10% propylene glycol, 0.6% diluted hydrochloric acid, and purified water, q.s.

*Description*

The pH of this elixir is 4.6-4.8 which is similar to that of the N. F. product. It is brown in color and cannot be distinguished in this respect from the N. F. elixir.

The newly formulated pentobarbital elixir does not require filtration and remains clear at both 25° C. and 4° C. An elixir which does not require filtration and remains clear at 25° C., but not at 4° C., may be prepared using only 45 parts sorbitol solution instead of the recommended 60 parts. However, since it is preferable for preparations to maintain their original appearance at colder temperatures, the inclusion of 60 parts sorbitol solution in the formula is recommended. It is noteworthy that Pentobarbital Elixir, N. F. X has a tendency to become slightly cloudy at colder temperatures, although this tendency is not as great as in Phenobarbital Elixir, U. S. P. XV.

*Bacteriological Testing*

Bacteriological testing indicated no need for the addition of preservatives for the same reason as stated for phenobarbital elixir.

*Taste Panel Studies*

Two panels of thirty individuals each were asked to participate in a taste comparison analysis of the newly formulated pentobarbital elixir and the N. F. elixir. There was no significant preference designated between the elixirs. Many panelists could not differentiate between them. The reason for this lack of differentiation and preference among many of the panelists was probably due to the unpleasant taste of the pentobarbital which actually "masks" the taste of the vehicle itself.

*Cost Analysis*

Cost analysis revealed that the cost * of the newly formulated pentobarbital elixir is $0.03 less per liter than Pentobarbital Elixir, N. F. X.

---

* Based on price quotations given in Oil, Paint and Drug Reporter, Nov. 1956.

## Summary

1. Improved formulas for phenobarbital and pentobarbital elixirs are suggested.

2. Elixirs prepared using the new formulas are similar in pH, appearance, and taste to Phenobarbital Elixir, U. S. P. XV, and Pentobarbital Elixir, N. F. X.

3. The newly formulated elixirs do not require filtration and remain clear at 25° C. and 4° C. In this respect, they have an advantage over the official formulas.

4. The new elixirs are lower in cost than Phenobarbital Elixir, U. S. P. XV, and Pentobarbital Elixir, N. F. X.

REFERENCES

(1) "The National Formulary", Tenth ed., J. B. Lippincott Co., Philadelphia, Pa., 1955, pp. 551-553.

(2) "The United States Pharmacopeia", First Supplement to the Fifteenth Rev., Mack Printing Co., Easton, Pa., 1956.

(3) "The National Formulary", Tenth ed., J. B. Lippincott Co., Philadelphia, Pa., 1955, p. 425.

(4) "The United States Pharmacopeia", Fifteenth Rev., Mack Printing Co., Easton, Pa., 1956, p. 482.

# SELECTED ABSTRACTS

**The Treatment of Capillary Fragility in the Aged With Bio-Flavonoids.** Sokoloff, B., Martin, W. C., and Saelhof, C. C. *J. Am. Geriat. Soc. 5*:306 (1957). The role of the bio-flavonoids in increasing the binding effect of the cement substance of the capillary walls has been recognized. The frequency of increased capillary fragility, particularly in elderly patients, is greater than had previously been recognized.

The authors found that, of 189 patients ranging in age from 53 to 88 years, 134 (64 per cent) demonstrated increased capillary fragility. The incidence was highest in hypertensive diabetics (100 per cent), next in hypertensive patients with cardiac involvement (77 percent), and third in hypertensive patients without serious cardiac involvement (72 per cent). Thirty patients with increased capillary fragility were treated with 200 mg. of bio-flavonoids three times a day for 4 weeks. In all but 3 cases the capillary fragility was restored to normal.

"Little strokes", representing dozens of small hemorrhages from the blood vessels of the brain, are probably one of the commonest diseases of aging man. In 13 patients with a history of such strokes, 600 mg. of bio-flavonoids were given daily for periods from 1 to 3 years. In 10 of these patients there were no indications of further "little strokes" during the period of treatment.

In a group of 45 patients with rheumatoid arthritis, bio-flavonoid therapy of 300 mg. or 600 mg. a day was instituted. Response was not satisfactory among patients having had the disease for a long period. However, there was substantial improvement in 20 of 33 cases in which the average duration of the disease was 6 or less years. Improvement was greatest among those having had the disease for the shortest time.

In 189 cases of retinitis of diabetic and hypertensive origin, bio-flavonoid therapy brought about prompt control and rapid absorption of the hemorrhage in 85 per cent of the cases. In another group of 45 patients with epistaxis, the epistaxis was arrested, usually within 36 hours, following intensive therapy with 1500 mg. of bio-flavonoids a day.

Thus, the authors concluded that bio-flavonoids are useful in the therapy of many of the chronic diseases of the aged.

**The Diuretic Activity of a New Oral Agent.** Clark, M. L., and Hagans, J. A. *J. Lab. and Clin. Med. 49:395* (1957). The comparative study of diuretic agents on nonedematous patients would seem to give a more stable and homogeneous basis for comparison. Therefore, the study reported by the authors was conducted on nonedematous patients.

The new oral diuretic aminoisometradine (1-methallyl-3-methyl-6-aminotetrahydropyrimidinedione), also known as Rolicton, was administered to 13 nonedematous patients in a dose of 1.2 Gm. a day and to 5 patients in a dose of 2.4 Gm. a day. Nine patients were given aminometramide (1-allyl-3-ethyl-6-aminotetrahydropyrimidinedione), also known as Mictine, in a dose of 1.2 Gm. a day. Sixteen patients received a placebo.

The authors reported that both of the oral diuretics produced a significant increase in urine volume and a loss of body weight, the maximum diuretic effect being achieved on the first day. This effect was compared with a control period during which neither drug was given. The placebo produced no such effect. The potency of the new compound appeared to be comparable to that of aminometramide. After withdrawal of the diuretic agents there was a diminished urine excretion and a gain in weight. This reaction added further to the evidence for the diuretic activity of the drugs. There was, however, a marked difference in the side effects from the two agents. Aminoisometradine produced no side effects, even in the double dose, but aminometramide frequently caused such side effects as nausea, anorexia, abdominal cramps, and vomiting.

---

**The Resistance of Oral Lactobacilli to Sodium Fluoride by In Vitro Testing Methods.** Green, G. E., and Dodd, M. C. *J. Am. Dent. Assoc. 54:654* (1957). The mode of action by which sodium fluoride reduces dental decay is not certain. Some have proposed that it inhibits acidogenic organisms, or acid production, or both. The authors studied the resistance of several strains of *Lactobacillus casei* to sodium fluoride when first isolated from the mouths of school children and following serial transfers in media containing increasingly higher concentrations of sodium fluoride.

It was found that the initial resistance to sodium fluoride varied from 0 to about 10,000 ppm sodium fluoride in modified Rogosa's SL agar medium. Following serial transfers, it was found that the re-

sistance of most of the strains to sodium fluoride could be increased. Some strains were capable of growing and producing acid in the presence of as much as 2 per cent sodium fluoride. As resistance developed there was some change in the colony and cellular morphology, but no apparent change in a series of fermentative characteristics.

From these findings, the authors concluded that it is unlikely that lactobacilli will come in contact with sufficient concentrations of sodium fluoride in the human oral cavity to significantly alter the acidogenic capacity or growth potential of the organisms. However, the effect of even slight changes in the acidogenic capacities on the cariogenic potential of oral lactobacilli is not certain.

---

**The Formation of Antibiotic Salts by Novobiocin.** Chaiet, L. and Wolf, F. J. *Antibiot. and Chemother. 7:*231 (1957). Novobiocin has been combined in clinical applications with many of the known antibiotics to provide varying degrees of synergism. However, the authors have found that novobiocin combines with all of the common basic antibiotics to form water insoluble salts of novobiocin. Antibiotics which are neutral, acidic, or amphoteric do not form water insoluble salts with novobiocin.

The authors combined a 10 per cent aqueous solution of the antibiotic with a 10 per cent aqueous solution of the monosodium salt of novobiocin. When a precipitate was formed, it was filtered, washed and dried. Later it was analyzed. The yields obtained were nearly quantitative.

The molar proportions found for the combinations of novobiocin with basic antibiotics were: streptomycin 3:1 (novobiocin 3: streptomycin 1), neomycin 6:1, spiramycin 1:1, viomycin 1:2, erythromycin 1:1, and eulicin 1:2. The solubility in water found for these combinations were; novobiocin-streptomycin, 0.8 mg./ml.; novobiocin-neomycin, 0.5 mg./ml.; novobiocin-spiramycin, 0.4 mg./ml.; novobiocin-viomycin, 1.1 mg./ml.; novobiocin-erythromycin, 0.3 mg./ml.; and novobiocin-eulicin, less than 1 mg./ml. Other characteristics of these salts were given.

Antibiotics having neutral, acidic or amphoteric properties did not form insoluble salts with novobiocin. These included, bacitracin, penicillin, synnematin, cycloserine, tetracycline, carbomycin, tyrothricin, and candicidin.

# American Journal of Pharmacy

The American Journal of Pharmacy is the oldest continuously published scientific periodical of its kind in America, having been established by the Philadelphia College of Pharmacy in 1825. After the original issue there were three other preliminary numbers until 1829, when regular publication began. From then until 1852 four issues were published annually, with the single exception of 1847, when an additional number appeared. Six issues a year were printed from 1853 to 1870, at which time the Journal became a monthly publication.

Former Editors of the Journal have been: Daniel B. Smith, 1825-1828; Benjamin Ellis, 1829-1831; Robert E. Griffith, 1831-1836; Joseph Carson, 1836-1850; William Procter, Jr., 1850-1871; John M. Maisch, 1871-1893; Henry Trimble, 1893-1898; Henry Kraemer, 1898-1917; George M. Beringer, 1917-1921, and Ivor Griffith, 1921-1941.

Established and maintained as a record of the progress of pharmacy and the allied sciences, the Journal's contents and policies are governed by an Editor and a Committee on Publications elected by the members of the College.

Manuscripts should be sent to the Editor, who does not assume any responsibility in connection with the views or investigations of contributors of accepted manuscripts, other than to exercise general care in selection.

Contributors are allowed a reasonable number of copies of this Journal, free of charge, if applied for when the proof is returned.

Reprints, if desired, should be ordered when the proof is returned. The table below shows the *approximate* cost of reprints, the make-up of the pages to be identically the same as in the Journal. The actual cost may vary from the figures given, and will depend upon the amount of presswork, paper, binding, and other factors. Reprints containing half-tones may be expected to cost somewhat more than the rates given.

| | 2 pp. | 4 pp. | 8 pp. | 16 pp. | Covers with Titles | |
|---|---|---|---|---|---|---|
| 50 copies..... | $ 4.50 | $10.00 | $16.25 | $27.50 | 50 copies..... | $ 7.50 |
| 100 " ..... | 7.50 | 13.75 | 21.25 | 40.00 | 100 " ..... | 12.50 |
| 250 " ..... | 10.00 | 17.50 | 27.50 | 53.75 | 250 " ..... | 17.50 |
| 500 " ..... | 15.00 | 25.00 | 35.00 | 68.75 | 500 " ..... | 26.25 |